

et al.
Agonist
6,268,342, which is a 371 of PCT/US97/14154, filed Aug.
27, 1997, which is a continuation-in-part of Ser. No.
08/705,790, filed Aug. 30, 1996, now abandoned. --

In the claims:

Please substitute the claim set in Appendix A entitled "Clean Version of Pending Claims" for the previously pending claim set. The specific amendment to claim 142 is as follows:

142 (Amended). A method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient, provided said fibrosis is not in the kidney, in the lung, in the liver, in the skin, of the central nervous system, in bone or bone marrow, in the cardiovascular system, in an endocrine organ, or in the gastro-intestinal system, and further provided that said fibrosis is not periportal fibrosis.

No new matter is being added by the foregoing amendments.

REMARKS

Reconsideration of the Office Action mailed August 14, 2001, (hereinafter "instant Office Action"), entry of the amendments hereinabove, and withdrawal of the rejection of claims 142 and 143 are respectfully requested. The amendment to claim 142 is made to further prosecution of the present application and is not intended to concede the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment which may be presented in any continuing application of the instant application.

In the instant Office Action, claims 142-143 are listed as pending and claims 142-143 are listed as rejected.

The 35 U.S.C. §101 Rejection

The Examiner has rejected claims 142 and 143 under 35 U.S.C. §101, alleging that claims 142 and 143 claim the same invention

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as that of claims 1-29 of prior U.S. Patent No. 6,268,342 (the '342 patent). Applicants respectfully traverse this rejection.

In order to support a double patenting rejection under 35 U.S.C. 101 it must be shown that an accused claim is drawn to identical subject matter as a claim of a prior patent. In this regard Applicants respectfully direct the Examiner's attention to MPEP §804, at paragraph II.A., *Statutory Double Patenting - 35 U.S.C. 101*, wherein it is stated:

In determining whether a statutory basis for a double patenting rejection exists, the question to be asked is: Is the same invention being claimed twice? 35 U.S.C. 101 prevents two patents from issuing on the same invention. "Same invention" means identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1984); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist. For example, the invention defined by a claim reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than "chlorine." On the other hand, claims may be differently worded and still define the same invention. Thus, a claim reciting a widget having a length of "36 inches" defines the same invention as a claim reciting the same widget having a length of "3 feet.";

(emphasis added.)

Applying the foregoing it can be seen that the statutory double patenting rejection levied by the Examiner can not stand since the claims of the '342 patent are not identical in scope to claims 42 and 43 of the instant application. Indeed such would be

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the case even if claims 42 and 43 were not amended as provided herein. However, notwithstanding the foregoing Applicants have amended claim 142 in order to remove literal overlap between the claimed subject matter of the instant application and that of the '342 patent.

To the extent that claims 1 - 29 of the '342 patent are themselves drawn to various aspects of the invention therein claimed, Applicants' arguments below have been likewise directed to several subsets of logically related claims.

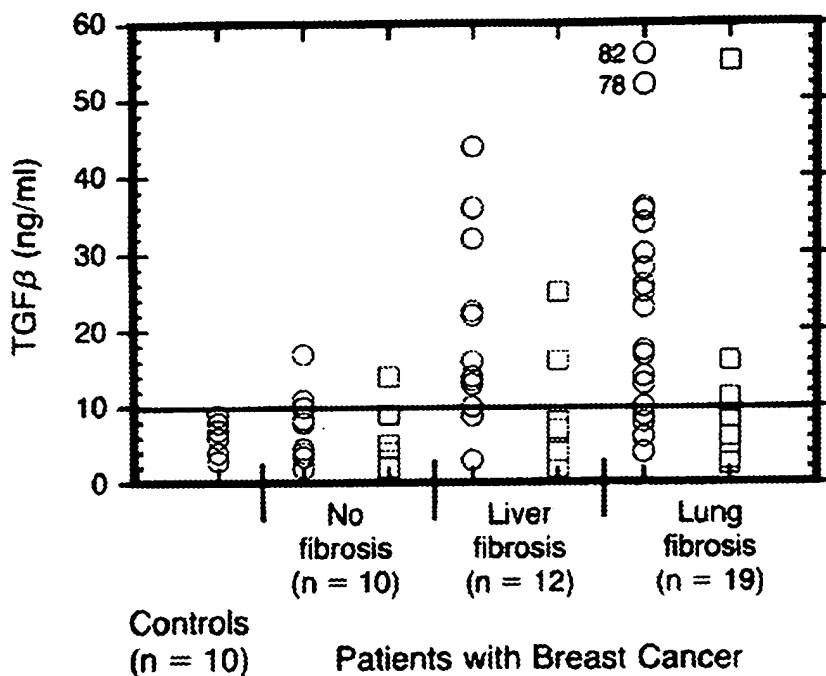
In respect of claims 11 - 16 of the '342 patent Applicants note that said claims are drawn to a method of *inhibiting over-expression of TGF- β* . In contrast, claims 42 and 43 of the instant application are drawn to a method of *inhibiting fibrosis*. As is well known in the art, inhibition of the over-expression of TGF- β is not identical to inhibition of fibrosis even though a correlation exists between the incidence of high levels of TGF- β and incidence of fibrosis.

To be clear in this regard Applicants note that Anscher, M.S., et al., (Transforming Growth Factor β as a Predictor of Liver and Lung Fibrosis after Autologous Bone Marrow Transplantation for Advanced Breast Cancer, N. Eng. J. Med., 328(22), 1592-98 (1993); hereinafter "Anscher"), teach that:

pretransplantation TGF β levels were significantly higher in patients in whom hepatic veno-occlusive disease or idiopathic interstitial pneumonitis developed than in the [control population] or the patients without these conditions. The predictive value for the development of either condition was 90 percent or more when pretransplantation plasma TGF β levels were more than 2 SD above the mean established in the controls,

(emphasis added). (See discussion in Anscher, under Results). Significantly in this regard are the data Anscher presents in support of the foregoing conclusion, depicted at figure 2 therein, reproduced below:

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Reviewing the data it is clear that while elevated TGF β levels are correlated to increased risk of fibrosis development, such risk does not reach 100%; i.e., not all individuals with elevated TGF β levels develop fibrosis. Indeed close inspection of figure 2 reveals that, of the 10 individuals in the "No fibrosis" group, at least 3 had TGF β values at or above the 2 SD level discussed in the foregoing passage, with at least one individual exceeding the 2 SD level quite dramatically. (TGF β = approx. 17 ng/ml vs. 2 SD level = 10 ng/ml).

For the Examiner's convenience a copy of Anscher is submitted herewith as Exhibit 1. (The Examiner will note that the copy of Anscher was retrieved from the New England Journal of Medicine web site, and that certain tables and figures were printed separately for the purposes of clarity.)

In light of the foregoing Applicants submit that the literal scope of claims 11 - 16 of the '342 patent is not identical to the literal scope of claims 42 and 43 of the instant application. Accordingly, withdrawal of the rejection of claims 42 and 43 of

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the instant application on the grounds of statutory double patenting, to the extent that such rejection is maintained over claims 11 - 16 of the '342 patent, is respectfully requested.

In respect of claims 26 - 29 of the '342 patent Applicants note that the literal scope of said claims encompasses *pharmaceutical compositions*. In contrast, the literal scope of claims 42 and 43 of the instant application encompasses a *method of treatment*, i.e., of inhibiting fibrosis in a patient. Thus the literal scope of claims 26 - 29 of the '342 patent is not identical to the literal scope of claims 42 and 43 of the instant application. Accordingly, withdrawal of the rejection of claims 42 and 43 of the instant application on the grounds of statutory double patenting, to the extent that such rejection is maintained over claims 26 - 29 of the '342 patent, is respectfully requested.

In respect of claim 1 of the '342 patent and the claims that depend directly or indirectly therefrom, (i.e., claims 3 - 8 and 17 - 20), Applicants note that the literal scope of said claims encompasses:

a method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin [sic, somatostatin] or a somatostatin [sic, somatostatin] agonist to said patient, wherein said fibrosis is in the kidney, in the lung, in the liver, in the skin, of the central nervous system, in bone or bone marrow, in the cardiovascular system, in an endocrine organ or in the gastro-intestinal system.

('342 patent, claim 1; emphasis added.). In contrast, the literal scope of claim 42 of the instant application, as presently amended, encompasses:

[a] method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient, provided said fibrosis is not in the kidney, in the lung, in the liver, in the skin, of the central nervous system, in bone or bone marrow, in the cardiovascular system, in an endocrine organ, or

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in the gastro-intestinal system, and further provided that said fibrosis is not periportal fibrosis.

(emphasis added). Claim 43 depends from claim 42 therefore amendment of claim 42 applies equally to claim 43.

As can be seen, Applicant's have amended claim 42 (and by extension, claim 43) in order to avoid overlap between the literal scope claim 42 and the literal scope of claim 1 (and by extension, claims 3-8 and 17 - 20) of the '342 patent. Accordingly, withdrawal of the rejection of claims 42 and 43 of the instant application on the grounds of statutory double patenting, to the extent that such rejection is maintained over claims 1, 3-8 and 17 - 20 of the '342 patent, is respectfully requested.

In respect of claim 2 of the '342 patent and the claims that depend directly or indirectly therefrom, (i.e., claims 9, 10 and 21 - 25), Applicants note that the literal scope of said claims encompasses:

a method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient, wherein said fibrosis is induced by chemotherapy, induced by radiation, induced by a drug or a combination of drugs, induced by a disease state, induced by an environmental or an industrial factor, induced by an immune reaction, or induced by a wound.

('342 patent, claim 1; emphasis added.). In contrast, and as discussed hereinabove, the literal scope of claim 42 of the instant application, as presently amended, encompasses:

[a] method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient, provided said fibrosis is not in the kidney, in the lung, in the liver, in the skin, of the central nervous system, in bone or bone marrow, in the cardiovascular system, in an endocrine organ, or in the gastro-intestinal system, and further provided that said fibrosis is not periportal fibrosis.

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(emphasis added). Again, claim 43 depends from claim 42 therefore amendment of claim 42 applies equally to claim 43.

Comparing the subject matter of claims 42 and 43 of the instant application to that of claims 2, 9, 10 and 21 - 25 of the '342 patent it can be seen that, whereas the former are concerned with the location of fibrosis to be treated (i.e., what organs or tissues are involved), the latter are concerned with inducements of fibrosis. As such the scope of claims 42 and 43 is not identical with the scope of any of claims 2, 9, 10 and 21 - 25 of the '342 patent. Accordingly, withdrawal of the rejection of claims 42 and 43 of the instant application on the grounds of statutory double patenting, to the extent that such rejection is maintained over claims 2, 9, 10 and 21 - 25 of the '342 patent, is respectfully requested.

The 35 U.S.C. §112 Rejection

The Examiner has rejected claim 143 under 35 U.S.C. §112, second paragraph, alleging that claim 143:

is substantially duplicative of claim 142. The claim does not further limit or define the antecedent claim (Instant Office Action, at page 2.). Applicants respectfully direct the Examiner's attention to the text of claim 142, which claims:

[a] method of inhibiting fibrosis in a patient said method comprising administering a therapeutically effective amount of somatostatin or a somatostatin agonist to said patient, ...

In contrast, claim 143 claims:

[a] method of claim 142, wherein said method comprises administering a therapeutically effective amount of a somatostatin agonist to said patient.

Thus contrary to the Examiner's allegation, claim 143 does indeed limit claim 142 since somatostatin has been removed from the genus of compounds to be utilized for treatment. Accordingly, withdrawal of the rejection of claims 43 under 35 U.S.C. §112, second paragraph, is respectfully requested.

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Other Matters

Applicants note that an Information Disclosure Statement was filed in the instant application on January 16, 2001. Applicants respectfully request that the Examiner include an initialed copy of Form 1449, submitted therewith, when the Examiner issues the next Office Action.

Applicants also note that claim 42, as amended herein, includes the limitation:

[...] and further provided that said fibrosis is not periportal fibrosis.

This limitation has been added in light of the disclosure of the Tracy, et al. reference (American Journal of Pathology, Vol. 143, No. 6, December 1993) which was made of record in Application No. 09/254,097; i.e., the direct parent application of the instant application. Indeed Tracy et al. is among the references cited in the foregoing Information Disclosure Statement.

Based upon the foregoing, Applicants believe that claims 142-143, as amended hereinabove, are in condition for allowance. Prompt and favorable action is earnestly solicited. The Examiner is invited to telephone Applicants' attorney at 508-478-0144 to facilitate prosecution of this application.

Respectfully submitted,

Date: 14. Feb. 02



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Serial Number: 09/761,605
Examiner: A. Davenport
Group Art: 1653

Attorney Docket 00537/149003

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Exhibit 1



The NEJM

2000-2005

Med. Rev. Rev.

Other

The New England Journal of Medicine

Volume 328

January 1993

Part 1

Editorial

Book

Review

You are invited to contribute to the NEJM's new online journal, *Journal of Clinical Investigation*, at www.jci.org. Visit our website for more information.

Journal of Clinical Investigation
Volume 100 Number 1 January 1993

Volume 328: 1992-1993 June 3, 1993 Number 22

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Transforming Growth Factor β as a Predictor of Liver and Lung Fibrosis after Autologous Bone Marrow Transplantation for Advanced Breast Cancer

Mitchell S. Ancker, William P. Peters, Herbert Baumhölzer, William P. Petros, and

Randy L. Jirtle

Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

ABSTRACT

Background: Hepatic veno-occlusive disease and idiopathic interstitial pneumonitis are major causes of morbidity and mortality after bone marrow transplantation. Fibrosis is a characteristic of both conditions, and transforming growth factor β (TGF β) has been implicated in the pathogenesis of fibrosis.

Methods: Using acid-ethanol extraction to remove TGF β from human plasma and a spin-lung epithelial-cell growth-inhibition assay to measure TGF β activity, we quantified plasma TGF β in 10 normal subjects and 41 patients before and after they underwent high-dose chemotherapy and autologous bone marrow transplantation for advanced breast cancer.

Results: There was no difference in pretransplantation TGF β levels between the controls and the patients who did not have hepatic veno-occlusive disease or idiopathic interstitial pneumonitis after transplantation. In contrast, pretransplantation TGF β levels were significantly higher in patients in whom hepatic veno-occlusive disease or idiopathic interstitial pneumonitis developed than in the controls or the patients without these conditions. The predictive value for the development of either condition was 90 percent or more when pretransplantation plasma TGF β levels were more than 2 SD above the mean established in the controls.

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The New English Journal of Medicine

GRUPO DE ESTUDOS SOBRE A CULTURA DA MUSICA

Translational Research for Advanced Biocatalysis

~~Wien, Sonntag, 9. Juli 1919. Gedacht an die Freiheit, 9. Juli 1919. 9. Juli 1919. 2. November.~~

STORY

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The level of this activity is often increased after bone marrow transplantation.
Conclusions. The plasma TGF β concentration measured after induction chemotherapy but before high-dose chemotherapy and autologous bone marrow transplantation strongly correlates with the risk of hepatic veno-occlusive disease and idiopathic interstitial pneumonitis after these treatments.

Hepatic veno-occlusive disease is a serious consequence of high-dose chemotherapy or radiotherapy combined with bone marrow transplantation for neoplasia; it occurs in 15 to 50 percent of patients, with a mortality rate of up to 50 percent.^{1,2,3,4,5,6,7} The syndrome typically develops one to three weeks after transplantation and is characterized by sudden weight gain, hepatomegaly, ascites, and hyperbilirubinemia;⁷ hepatic encephalopathy may also develop.

Similarly, pulmonary complications of bone marrow-transplantation are a major source of morbidity, occurring in 40 to 60 percent of patients.⁸ Noninfectious pulmonary complications (idiopathic interstitial pneumonitis) occur in 10 to 25 percent of bone marrow-transplant recipients.⁹ This syndrome is characterized by dyspnea, fever, and hypoxemia, with or without diffuse interstitial infiltrates on chest radiography. It occurs 40 to 75 days after transplantation; the mortality rates are high. Both the chemotherapy and the radiotherapy used in the conditioning regimens have been implicated in the development of liver and lung damage after bone marrow transplantation.^{1,8,9}

Fibrosis is a prominent feature in both the lungs and the liver in patients with these complications.^{10,11} Recently, efforts have been directed at elucidating the molecular mechanisms of these fibrotic reactions. Transforming growth factor β (TGF β) stimulates fibroblasts to migrate to the site of injury, proliferate, and produce collagen; it also inhibits collagen degradation.¹² Thus, it plays an important part in normal wound healing¹³⁻¹⁴ as well as in abnormal fibrogenesis. TGF β has been implicated in the causation of chronic pulmonary fibrosis in rats and mice exposed to bleomycin or cyclophosphamide,^{15,16,17,18,19,20} and in the development of hepatic fibrosis in rats exposed to radiation²¹ or carbon tetrachloride.^{22,23} TGF β may also have a role in fibrotic liver and lung diseases in humans,^{24,25,26,27} such as chronic hepatitis,²⁸ idiopathic pulmonary fibrosis,^{29,30} and systemic sclerosis.^{31,32,33} Inhibition of TGF β activity can prevent the development of chronic hepatitis,²⁸ acute mesangial proliferative glomerulonephritis,³⁴ and the fibrotic effects of carbon tetrachloride,³⁵ providing further evidence for the role of TGF β in these fibrotic conditions.

Because the level of expression of the gene for TGF $\beta 1$ is elevated in both animals and humans with fibrotic liver or lung diseases,^{28,30} we postulated that an increase in the release and activation of TGF $\beta 1$ in fibrotic tissue would also result in an increase in the circulating level of this growth factor. It may be possible to use the plasma concentration of TGF β proteins measured before the administration of high-dose chemotherapy to identify patients most prone to the development of lung or liver injury after bone marrow transplantation.

Methods

Patients

People under 40 years of age have more bone mineral than those over 40 years of age. This is because bone mineral increases until about 40 years of age and then begins to decrease.

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and the other to the people of the land, so as to cause them to conceive of the
King as a wise and good ruler who has the welfare of his subjects at heart.

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Examiners testicular function need to measure LH and/or FSH or sex-hormones.

act draft, dated 1998-07-10, available at <http://www.legis.state.vt.us/legisweb/billinfo/146/146-1000.htm>.

98 In 1990, the U.S. Congress passed the Americans with Disabilities Act (ADA).

Household members who have been granted permanent residence status

11. *Glomerulocapillaryitis with crescent formation is associated with IgA1 nephropathy.*

For more information about the study, contact Dr. Michael J. Hwang at (319) 356-4000 or email at mhwang@uiowa.edu.

Post-flight to non-instrumented sites selected because they included DDT. To understand more about what might lead to great loss of diversity from disturbed habitats or regeneration areas, see also the next section.

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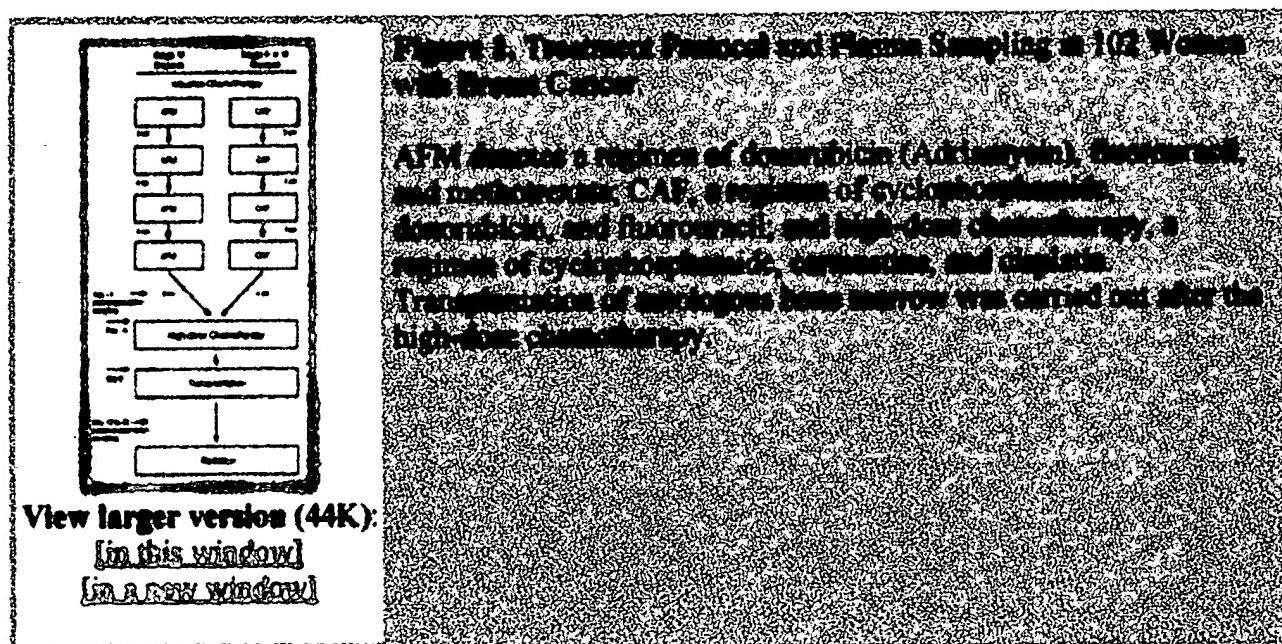
1981-1982 Field Measurements of the Riverbed

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At the time of this analysis, 102 women with adenocarcinoma of the breast had been treated according to research protocols for bone marrow transplantation at Duke University Medical Center. All patients had either stage IV disease (metastases) or advanced stage II or III disease (more than 10 positive lymph nodes found after axillary dissection) and underwent four cycles of induction chemotherapy followed by high-dose chemotherapy and autologous bone marrow transplantation (Figure 1). The details of this treatment regimen have been previously reported.²² In brief, the induction regimen consisted of cyclophosphamide, doxorubicin (Adriamycin), and fluorouracil (for stage II or III disease) or doxorubicin, fluorouracil, and methotrexate (for stage IV disease). The high-dose chemotherapy consisted of carbustine, cyclophosphamide, and cisplatin. Radiation therapy was directed at the sites of known metastases (stage IV disease) or to the ipsilateral chest wall, internal mammary nodes, and supravacular lymph nodes (stage II or III disease) after autologous bone marrow transplantation.



Of the 102 patients treated, 12 subsequently had hepatic veno-occlusive disease, 19 had pulmonary fibrosis, and the remaining 71 had neither. Both conditions were defined clinically. Hepatic veno-occlusive disease was indicated by the development of weight gain, hepatomegaly, ascites, and hyperbilirubinemia one to three weeks after transplantation. Pulmonary fibrosis was indicated by dyspnea, fever, and hypoxemia with or without diffuse interstitial infiltrates on chest radiography, beginning 40 to 75 days after transplantation. Other causes of these two syndromes had to be excluded in order to accept these diagnoses. Biopsy was not required. All patients with hepatic veno-occlusive disease or pulmonary fibrosis were included in this analysis. A sample of 10 patients who had neither condition (a sample matching the number of controls, described below) was randomly selected from among all patients enrolled under these protocols whose plasma samples were stored in the archives of the cryopreservation laboratory. Specimens were coded, and TGF β levels measured, without the investigators' prior knowledge of whether or not the patient had hepatic veno-occlusive disease or pulmonary fibrosis. After the plasma TGF β levels in the samples were measured, the code was broken and the data were grouped for analysis according to the patients' status for toxic complications (see below).

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Figure 1. Tectonic map of the Western Cape Province showing the location of the Cape Fold Belt.

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7. *La längerer Revue* (444)

**Stage IV
Disease**

**Stage II or III
Disease**

Induction Chemotherapy

AFM

CAF

3 wk

3 wk

AFM

CAF

3 wk

3 wk

AFM

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3 wk

3 wk

AFM

CAF

**Day -7:
pretransplantation
sampling**

Day -6

High-Dose Chemotherapy

Day 0

Transplantation

**Day 12 to 37: →
post-transplantation
sampling**

Radiation

Anscher Fig. 1

In addition, a third sample was taken at the time of bone marrow transplantation. Plasma samples were obtained twice. The first sample was obtained after induction chemotherapy but before the administration of high-dose chemotherapy and autologous bone marrow transplantation. The second sample was obtained after the high-dose chemotherapy and transplantation (Figure 1), between 12 and 37 days after the operation, depending on the availability of adequate samples. The findings in the transplant recipients were compared with those in controls — 10 normal blood donors whose plasma was obtained from the American Red Cross (Charlotte, N.C.).

Extraction of TGF β from Plasma

TGF β was extracted from plasma by acid-ethanol extraction^{37,38}. Because this extraction procedure activates TGF β , we could not determine the amount of active and inactive TGF β present in the samples. To extract TGF β , 4 ml of an acid-ethanol solution (375 ml of 95 percent ethanol, 7.5 ml of 12 N hydrochloric acid, 33 mg of phenylmethylsulfonyl fluoride, and 1.9 mg of pepstatin) was added to a 1-ml plasma sample previously diluted by a factor of 2 with distilled water. The samples were incubated overnight at 4 °C, then centrifuged at 20,000 × g for 30 minutes at 4 °C. The supernatant was removed and stored at 4 °C, and the remainder of the sample was reextracted and centrifuged. The two supernatants were then combined, and the pH was adjusted to 5.2 to 5.3 with ammonium hydroxide. One milliliter of 2 M ammonium hydroxide was added to 85 ml of supernatant and diluted by a factor of 3 with cold (4 °C) 100 percent ethanol. This solution was incubated at -20 °C for at least two days and then centrifuged. The pellet was resuspended in 5 ml of 1 M acetic acid, dialyzed overnight in 1 percent acetic acid, divided into aliquots, lyophilized, and stored at -20 °C until assayed.

Assay for TGF β

Plasma levels of TGF β were quantified with the use of an assay measuring the inhibition of the growth of mink lung epithelial cells³⁹. Because this assay is not capable of discriminating among the three isoforms of TGF β , throughout this paper we simply use the term "TGF β ." In brief, after the MV 1 Lu mink-lung epithelial cells (CCL-64) were subjected to trypsinization and suspended in the assay medium, they were plated at a concentration of 10^5 cells per milliliter. After incubation at 37 °C for 1 hour, TGF β test samples and standards of known TGF β 1 concentration were added to the wells and incubated at 37 °C for 22 hours. The extent of DNA synthesis was then determined by incubating the cells with 3 H-labeled thymidine at 37 °C for an additional four hours. The cells were finally fixed for one hour at room temperature in 1.0 ml of methanol-acetic acid solution (3:1 vol/vol) and washed twice in 50 percent methanol. They were then solubilized in 0.3 N sodium hydroxide, and the radiolabeled DNA was extracted by precipitation with trichloroacetic acid. The amount of radioactivity in the cells exposed to the test samples and TGF β 1 standards was determined with a liquid-scintillation counter. This assay was able to detect amounts of TGF β ranging from 0.05 to 0.5 ng per milliliter ($0.3 \text{ to } 2 \times 10^{-8}$ nmol per liter), with 50 percent inhibition occurring at a concentration of 0.1 ng per milliliter (0.4×10^{-8} nmol per liter). The samples were serially diluted until the quantities of TGF β present were in the linear portion of the sigmoid-shaped curve for the TGF β standard. Actual TGF β levels were then calculated by multiplying the measured TGF β concentration by the dilution factor. Test samples were always assayed with samples containing known quantities of TGF β to ensure the reliability of the bioassay.

“I am not a member of any particular party,” he said. “I am a member of the Constitution.”

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To determine whether the inhibitory effect of the test samples was due specifically to TGF β , a neutralizing antibody that recognized TGF β (R&D Systems, Minneapolis) was added to all the test samples one hour before they were added to the mink-lung cells. Because the antibody was not specific for an individual isoform of TGF β , we could not determine the relative contributions of the three isoforms to the total plasma concentration. In all test samples the TGF β antibody was able to neutralize completely the inhibition of 50 percent of the cell growth (data not shown).

Statistical Analysis

Plasma TGF β was measured in the controls and patients both before and after bone marrow transplantation. Analysis of variance and Scheffe's method of multiple comparisons were used to compare mean values determined before and after transplantation in patients according to whether they subsequently had hepatic veno-occlusive disease, pulmonary fibrosis, or neither condition. Sensitivity, specificity, and predictive values (positive and negative) were calculated on the basis of a cutoff value for plasma TGF β of 10 ng per milliliter (4×10^{-7} mmol per liter), which was 2 SD above the mean determined in the controls (6 ng per milliliter [2.4×10^{-7} mmol per liter]).

The clinical variables determined in each patient are shown in Table 1. These data were analyzed in the same way as the TGF β measurements.¹⁹ No clinical information was available for the controls because they were anonymous blood donors. Laboratory values were measured on or as close as possible to the dates on which plasma samples were obtained for measurement of TGF β (Figure 1), to determine whether there were any differences between the patients in whom hepatic veno-occlusive disease or pulmonary fibrosis developed and the patients without these complications.

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Table 1. Clinical Characteristics Determined in 102 Women with Breast Cancer.

Results

The characteristics of the 41 patients who underwent autologous bone marrow transplantation for advanced breast cancer are shown in Table 2. The patients in whom pulmonary fibrosis or hepatic veno-occlusive disease later developed and the patients without these complications were similar in all respects except that the group with hepatic veno-occlusive disease included patients with distant metastases who had received chemotherapy or radiotherapy before they were enrolled in the transplantation program. The mortality rates for pulmonary fibrosis and hepatic veno-occlusive disease were 26 percent and 17 percent, respectively (Table 2).

Review & Testimony

Table 3: Chinese Government Employees in 103 Major Cities

શ્રીબ્રહ્મ

Hematologic factors†

- White-cell count
- Hemoglobin
- Hematocrit
- Platelet count
- Prothrombin time
- Activated partial-thromboplastin time

Biochemical factors†

- Uric acid
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Blood urea nitrogen
- Creatinine
- Calcium
- Magnesium
- Phosphorus
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Lactate dehydrogenase
- Total bilirubin
- Direct bilirubin

Pulmonary function (measured before induction chemotherapy or transplantation)

- Forced vital capacity
- Forced expiratory volume in one second
- Vital capacity
- Total lung capacity
- Carbon monoxide diffusion capacity
- Expiratory reserve volume
- Functional residual capacity

Treatment factors

- Previous chemotherapy before enrollment for transplantation
- Previous radiation therapy before enrollment for transplantation
- Use of peripheral-blood-cell progenitors during transplantation
- Duration of carmustine infusion during transplantation
- Use of colony-stimulating factor during transplantation

Tumor factors

- Maximal tumor size at diagnosis
- Number of positive nodes at diagnosis

Pharmacokinetics (high-dose chemotherapy only)

- Area under the concentration-time curve for carmustine and cyclophosphamide (data not available for cisplatin)

*There were no significant differences in the mean values for these clinical factors between the group of patients who did not have toxic complications and the groups that did ($P>0.1$ in all cases).

†Hematologic and biochemical factors were measured on or as close as possible to the dates on which plasma samples were obtained for measurement of TGF β .

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1. *Chlorophytum comosum* (L.) Willd. (Asparagaceae) - *Chlorophytum comosum* (L.) Willd. (Asparagaceae)

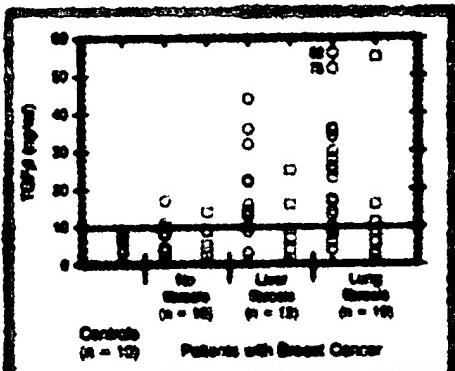
La phonie
s'explique par la
position des lèvres et des dents.
Le son de la phonie dépend de la position
des lèvres et des dents.

1. WILHELM
2. WILHELM

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Table 2. Characteristics of Patients Undergoing Autologous Bone Marrow Transplantation for Breast Cancer.

The TGF β concentrations in each patient and control are shown in Figure 2; the solid line at 10 ng per milliliter represents the TGF β level 2 SD above the mean value of 6.1 ng per milliliter (2.4×10^{-7} nmol per liter) determined in the controls (10 healthy blood donors). The mean TGF β concentrations in each study group are shown in Figure 3. When we compared the TGF β levels measured in the patients before transplantation with the levels in the controls, we found no significant difference ($P > 0.1$) between the controls and the patients who did not have hepatic veno-occlusive disease or pulmonary fibrosis after transplantation. In contrast, the pretransplantation TGF β levels in patients who later had hepatic veno-occlusive disease or pulmonary fibrosis were significantly higher ($P = 0.003$) than those in the controls and the patients without fibrotic changes in their lungs or liver.



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Figure 2. Individual Pretransplant TGF β Pretransplant Concentrations in the Control Group and Groups.

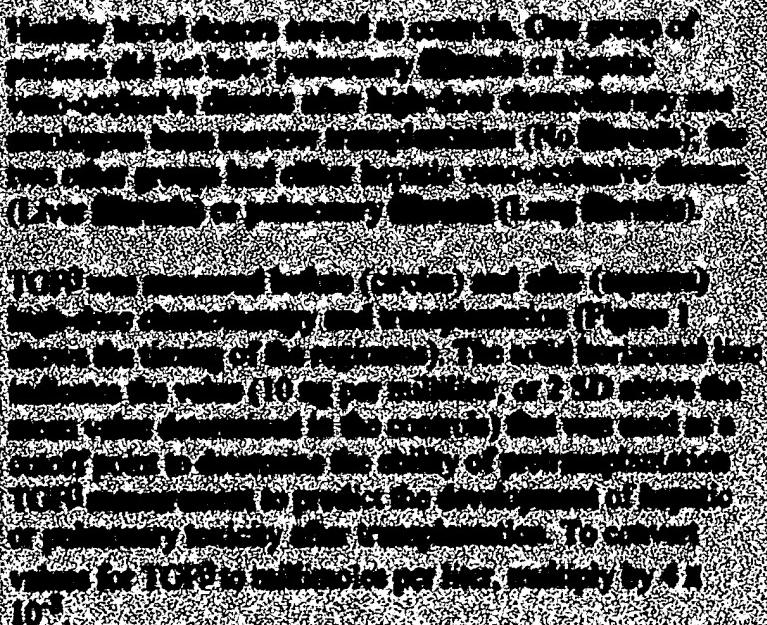
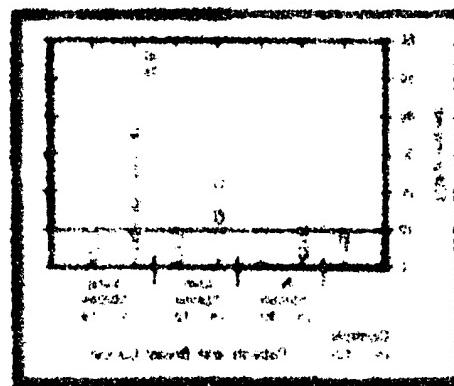


Table 5. Correspondence to Previous Unpublished Analogous Bone Morphologies for Differentiation to Fetal Callus.

1. **What is the difference between TGF- β 1 and TGF- β 2 in terms of their biological activities?**

Highly visible as being the most basic of all categories. One group of
such categories is that of the pure or basic types of inference, which
are called *monocategoreical* or *monocategoreic*. The other group
of such categories is that of the mixed or hybrid types of inference,
which are called *polycategoreical* or *polycategoreic*.

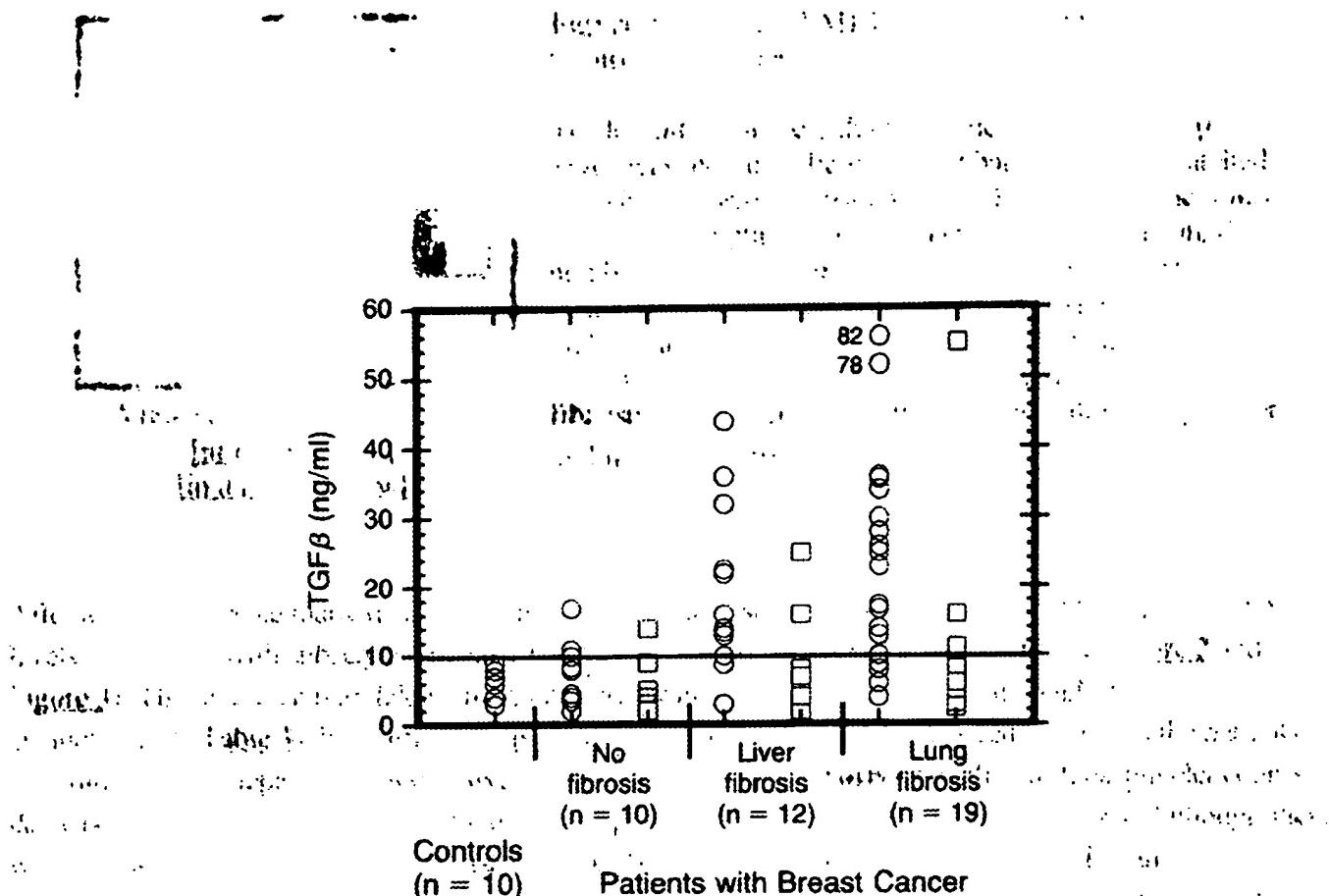


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2. **תְּמִימָה** בְּלֵבֶן

| VARIABLE | PATIENTS WITHOUT FIBROSIS (N = 10) | PATIENTS WITH FIBROSIS | |
|---|---|---------------------------|----------|
| | LIVER (N = 12) | LUNGS (N = 19) | |
| Age (yr) | | | |
| Mean | 41 | 40 | 39 |
| Range | 32-53 | 32-46 | 30-47 |
| Tumor size (cm)* | | | |
| Mean | 4.2 | 4.2 | 3.4 |
| Range | 1.2-12 | 2-11 | 1-10 |
| No. of positive nodes | | | |
| Mean | 15 | 12 | 14 |
| Range | 10-39 | 0-33 | 10-33 |
| Patients given chemotherapy before enrollment for transplantation (%) | 0 | 5 (42) | 0 |
| Patients given previous radiation therapy (%) | 0 | 2 (17) | 0 |
| Patients with distant metastases (%) | | | |
| No metastases | 10 | 6 (50) | 19 (100) |
| Lung | 0 | 0 | 0 |
| Liver | 0 | 2 (17) | 0 |
| Other site | 0 | 4 (33) | 0 |
| Patients dying of toxic complications (%) | — | 2 (17) | 5 (26) |

*Measured before induction chemotherapy.

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| both in | and I | I shall | the same next | |
| with a lot | There | you are | time to go | |
| from me | you're | you're | there | |

Table 6
Comparison of
the Results of
the Various
Experiments

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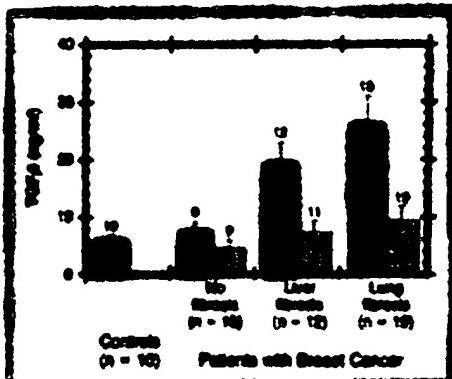
7

| Year | Officer | Rank | Age | Length of Service | Number of Cases | Number of Convictions | Percentage of Convictions |
|------|-----------------|-------|-----|-------------------|-----------------|-----------------------|---------------------------|
| 1850 | John C. Frémont | Major | 35 | 1 year | 10 | 8 | 80% |
| 1851 | John C. Frémont | Major | 36 | 2 years | 15 | 12 | 80% |
| 1852 | John C. Frémont | Major | 37 | 3 years | 20 | 16 | 80% |
| 1853 | John C. Frémont | Major | 38 | 4 years | 25 | 20 | 80% |
| 1854 | John C. Frémont | Major | 39 | 5 years | 30 | 24 | 80% |
| 1855 | John C. Frémont | Major | 40 | 6 years | 35 | 28 | 80% |
| 1856 | John C. Frémont | Major | 41 | 7 years | 40 | 32 | 80% |
| 1857 | John C. Frémont | Major | 42 | 8 years | 45 | 36 | 80% |
| 1858 | John C. Frémont | Major | 43 | 9 years | 50 | 40 | 80% |
| 1859 | John C. Frémont | Major | 44 | 10 years | 55 | 44 | 80% |
| 1860 | John C. Frémont | Major | 45 | 11 years | 60 | 48 | 80% |
| 1861 | John C. Frémont | Major | 46 | 12 years | 65 | 52 | 80% |
| 1862 | John C. Frémont | Major | 47 | 13 years | 70 | 56 | 80% |
| 1863 | John C. Frémont | Major | 48 | 14 years | 75 | 60 | 80% |
| 1864 | John C. Frémont | Major | 49 | 15 years | 80 | 64 | 80% |
| 1865 | John C. Frémont | Major | 50 | 16 years | 85 | 68 | 80% |
| 1866 | John C. Frémont | Major | 51 | 17 years | 90 | 72 | 80% |
| 1867 | John C. Frémont | Major | 52 | 18 years | 95 | 76 | 80% |
| 1868 | John C. Frémont | Major | 53 | 19 years | 100 | 80 | 80% |
| 1869 | John C. Frémont | Major | 54 | 20 years | 105 | 84 | 80% |
| 1870 | John C. Frémont | Major | 55 | 21 years | 110 | 88 | 80% |
| 1871 | John C. Frémont | Major | 56 | 22 years | 115 | 92 | 80% |
| 1872 | John C. Frémont | Major | 57 | 23 years | 120 | 96 | 80% |
| 1873 | John C. Frémont | Major | 58 | 24 years | 125 | 100 | 80% |
| 1874 | John C. Frémont | Major | 59 | 25 years | 130 | 104 | 80% |
| 1875 | John C. Frémont | Major | 60 | 26 years | 135 | 108 | 80% |
| 1876 | John C. Frémont | Major | 61 | 27 years | 140 | 112 | 80% |
| 1877 | John C. Frémont | Major | 62 | 28 years | 145 | 116 | 80% |
| 1878 | John C. Frémont | Major | 63 | 29 years | 150 | 120 | 80% |
| 1879 | John C. Frémont | Major | 64 | 30 years | 155 | 124 | 80% |
| 1880 | John C. Frémont | Major | 65 | 31 years | 160 | 128 | 80% |
| 1881 | John C. Frémont | Major | 66 | 32 years | 165 | 132 | 80% |
| 1882 | John C. Frémont | Major | 67 | 33 years | 170 | 136 | 80% |
| 1883 | John C. Frémont | Major | 68 | 34 years | 175 | 140 | 80% |
| 1884 | John C. Frémont | Major | 69 | 35 years | 180 | 144 | 80% |
| 1885 | John C. Frémont | Major | 70 | 36 years | 185 | 148 | 80% |
| 1886 | John C. Frémont | Major | 71 | 37 years | 190 | 152 | 80% |
| 1887 | John C. Frémont | Major | 72 | 38 years | 195 | 156 | 80% |
| 1888 | John C. Frémont | Major | 73 | 39 years | 200 | 160 | 80% |
| 1889 | John C. Frémont | Major | 74 | 40 years | 205 | 164 | 80% |
| 1890 | John C. Frémont | Major | 75 | 41 years | 210 | 168 | 80% |
| 1891 | John C. Frémont | Major | 76 | 42 years | 215 | 172 | 80% |
| 1892 | John C. Frémont | Major | 77 | 43 years | 220 | 176 | 80% |
| 1893 | John C. Frémont | Major | 78 | 44 years | 225 | 180 | 80% |
| 1894 | John C. Frémont | Major | 79 | 45 years | 230 | 184 | 80% |
| 1895 | John C. Frémont | Major | 80 | 46 years | 235 | 188 | 80% |
| 1896 | John C. Frémont | Major | 81 | 47 years | 240 | 192 | 80% |
| 1897 | John C. Frémont | Major | 82 | 48 years | 245 | 196 | 80% |
| 1898 | John C. Frémont | Major | 83 | 49 years | 250 | 200 | 80% |
| 1899 | John C. Frémont | Major | 84 | 50 years | 255 | 204 | 80% |
| 1900 | John C. Frémont | Major | 85 | 51 years | 260 | 208 | 80% |
| 1901 | John C. Frémont | Major | 86 | 52 years | 265 | 212 | 80% |
| 1902 | John C. Frémont | Major | 87 | 53 years | 270 | 216 | 80% |
| 1903 | John C. Frémont | Major | 88 | 54 years | 275 | 220 | 80% |
| 1904 | John C. Frémont | Major | 89 | 55 years | 280 | 224 | 80% |
| 1905 | John C. Frémont | Major | 90 | 56 years | 285 | 228 | 80% |
| 1906 | John C. Frémont | Major | 91 | 57 years | 290 | 232 | 80% |
| 1907 | John C. Frémont | Major | 92 | 58 years | 295 | 236 | 80% |
| 1908 | John C. Frémont | Major | 93 | 59 years | 300 | 240 | 80% |
| 1909 | John C. Frémont | Major | 94 | 60 years | 305 | 244 | 80% |
| 1910 | John C. Frémont | Major | 95 | 61 years | 310 | 248 | 80% |
| 1911 | John C. Frémont | Major | 96 | 62 years | 315 | 252 | 80% |
| 1912 | John C. Frémont | Major | 97 | 63 years | 320 | 256 | 80% |
| 1913 | John C. Frémont | Major | 98 | 64 years | 325 | 260 | 80% |
| 1914 | John C. Frémont | Major | 99 | 65 years | 330 | 264 | 80% |
| 1915 | John C. Frémont | Major | 100 | 66 years | 335 | 268 | 80% |
| 1916 | John C. Frémont | Major | 101 | 67 years | 340 | 272 | 80% |
| 1917 | John C. Frémont | Major | 102 | 68 years | 345 | 276 | 80% |
| 1918 | John C. Frémont | Major | 103 | 69 years | 350 | 280 | 80% |
| 1919 | John C. Frémont | Major | 104 | 70 years | 355 | 284 | 80% |
| 1920 | John C. Frémont | Major | 105 | 71 years | 360 | 288 | 80% |
| 1921 | John C. Frémont | Major | 106 | 72 years | 365 | 292 | 80% |
| 1922 | John C. Frémont | Major | 107 | 73 years | 370 | 296 | 80% |
| 1923 | John C. Frémont | Major | 108 | 74 years | 375 | 300 | 80% |
| 1924 | John C. Frémont | Major | 109 | 75 years | 380 | 304 | 80% |
| 1925 | John C. Frémont | Major | 110 | 76 years | 385 | 308 | 80% |
| 1926 | John C. Frémont | Major | 111 | 77 years | 390 | 312 | 80% |
| 1927 | John C. Frémont | Major | 112 | 78 years | 395 | 316 | 80% |
| 1928 | John C. Frémont | Major | 113 | 79 years | 400 | 320 | 80% |
| 1929 | John C. Frémont | Major | 114 | 80 years | 405 | 324 | 80% |
| 1930 | John C. Frémont | Major | 115 | 81 years | 410 | 328 | 80% |
| 1931 | John C. Frémont | Major | 116 | 82 years | 415 | 332 | 80% |
| 1932 | John C. Frémont | Major | 117 | 83 years | 420 | 336 | 80% |
| 1933 | John C. Frémont | Major | 118 | 84 years | 425 | 340 | 80% |
| 1934 | John C. Frémont | Major | 119 | 85 years | 430 | 344 | 80% |
| 1935 | John C. Frémont | Major | 120 | 86 years | 435 | 348 | 80% |
| 1936 | John C. Frémont | Major | 121 | 87 years | 440 | 352 | 80% |
| 1937 | John C. Frémont | Major | 122 | 88 years | 445 | 356 | 80% |
| 1938 | John C. Frémont | Major | 123 | 89 years | 450 | 360 | 80% |
| 1939 | John C. Frémont | Major | 124 | 90 years | 455 | 364 | 80% |
| 1940 | John C. Frémont | Major | 125 | 91 years | 460 | 368 | 80% |
| 1941 | John C. Frémont | Major | 126 | 92 years | 465 | 372 | 80% |
| 1942 | John C. Frémont | Major | 127 | 93 years | 470 | 376 | 80% |
| 1943 | John C. Frémont | Major | 128 | 94 years | 475 | 380 | 80% |
| 1944 | John C. Frémont | Major | 129 | 95 years | 480 | 384 | 80% |
| 1945 | John C. Frémont | Major | 130 | 96 years | 485 | 388 | 80% |
| 1946 | John C. Frémont | Major | 131 | 97 years | 490 | 392 | 80% |
| 1947 | John C. Frémont | Major | 132 | 98 years | 495 | 396 | 80% |
| 1948 | John C. Frémont | Major | 133 | 99 years | 500 | 400 | 80% |
| 1949 | John C. Frémont | Major | 134 | 100 years | 505 | 404 | 80% |
| 1950 | John C. Frémont | Major | 135 | 101 years | 510 | 408 | 80% |
| 1951 | John C. Frémont | Major | 136 | 102 years | 515 | 412 | 80% |
| 1952 | John C. Frémont | Major | 137 | 103 years | 520 | 416 | 80% |
| 1953 | John C. Frémont | Major | 138 | 104 years | 525 | 420 | 80% |
| 1954 | John C. Frémont | Major | 139 | 105 years | 530 | 424 | 80% |
| 1955 | John C. Frémont | Major | 140 | 106 years | 535 | 428 | 80% |
| 1956 | John C. Frémont | Major | 141 | 107 years | 540 | 432 | 80% |
| 1957 | John C. Frémont | Major | 142 | 108 years | 545 | 436 | 80% |
| 1958 | John C. Frémont | Major | 143 | 109 years | 550 | 440 | 80% |
| 1959 | John C. Frémont | Major | 144 | 110 years | 555 | 444 | 80% |
| 1960 | John C. Frémont | Major | 145 | 111 years | 560 | 448 | 80% |
| 1961 | John C. Frémont | Major | 146 | 112 years | 565 | 452 | 80% |
| 1962 | John C. Frémont | Major | 147 | 113 years | 570 | 456 | 80% |
| 1963 | John C. Frémont | Major | 148 | 114 years | 575 | 460 | 80% |
| 1964 | John C. Frémont | Major | 149 | 115 years | 580 | 464 | 80% |
| 1965 | John C. Frémont | Major | 150 | 116 years | 585 | 468 | 80% |
| 1966 | John C. Frémont | Major | 151 | 117 years | 590 | 472 | 80% |
| 1967 | John C. Frémont | Major | 152 | 118 years | 595 | 476 | 80% |
| 1968 | John C. Frémont | Major | 153 | 119 years | 600 | 480 | 80% |
| 1969 | John C. Frémont | Major | 154 | 120 years | 605 | 484 | 80% |
| 1970 | John C. Frémont | Major | 155 | 121 years | 610 | 488 | 80% |
| 1971 | John C. Frémont | Major | 156 | 122 years | 615 | 492 | 80% |
| 1972 | John C. Frémont | Major | 157 | 123 years | 620 | 496 | 80% |
| 1973 | John C. Frémont | Major | 158 | 124 years | 625 | 500 | 80% |
| 1974 | John C. Frémont | Major | 159 | 125 years | 630 | 504 | 80% |
| 1975 | John C. Frémont | Major | 160 | 126 years | 635 | 508 | 80% |
| 1976 | John C. Frémont | Major | 161 | 127 years | 640 | 512 | 80% |
| 1977 | John C. Frémont | Major | 162 | 128 years | 645 | 516 | 80% |
| 1978 | John C. Frémont | Major | 163 | 129 years | 650 | 520 | 80% |
| 1979 | John C. Frémont | Major | 164 | 130 years | 655 | 524 | 80% |
| 1980 | John C. Frémont | Major | 165 | 131 years | 660 | 528 | 80% |
| 1981 | John C. Frémont | Major | 166 | 132 years | 665 | 532 | 80% |
| 1982 | John C. Frémont | Major | 167 | 133 years | 670 | 536 | 80% |
| 1983 | John C. Frémont | Major | 168 | 134 years | 675 | 540 | 80% |
| 1984 | John C. Frémont | Major | 169 | 135 years | 680 | 544 | 80% |
| 1985 | John C. Frémont | Major | 170 | 136 years | 685 | 548 | 80% |
| 1986 | John C. Frémont | Major | 171 | 137 years | 690 | 552 | 80% |
| 1987 | John C. Frémont | Major | 172 | 138 years | 695 | 556 | 80% |
| 1988 | John C. Frémont | Major | 173 | 139 years | 700 | 560 | 80% |
| 1989 | John C. Frémont | Major | 174 | 140 years | 705 | 564 | 80% |
| 1990 | John C. Frémont | Major | 175 | 141 years | 710 | 568 | 80% |
| 1991 | John C. Frémont | Major | 176 | 142 years | 715 | 572 | 80% |
| 1992 | John C. Frémont | Major | 177 | 143 years | 720 | 576 | 80% |
| 1993 | John C. Frémont | Major | 178 | 144 years | 725 | 580 | 80% |
| 1994 | John C. Frémont | Major | 179 | 145 years | 730 | 584 | 80% |
| 1995 | John C. Frémont | Major | 180 | 146 years | 735 | 588 | 80% |
| 1996 | John C. Frémont | Major | 181 | 147 years | 740 | 592 | 80% |
| 1997 | John C. Frémont | Major | 182 | 148 years | 745 | 596 | 80% |
| 1998 | John C. Frémont | Major | 183 | 149 years | 750 | 600 | 80% |
| 1999 | John C. Frémont | Major | 184 | 150 years | 755 | 604 | 80% |
| 2000 | John C. Frémont | Major | 185 | 151 years | 760 | 608 | 80% |
| 2001 | John C. Frémont | Major | 186 | 152 years | 765 | 612 | 80% |
| 2002 | John C. Frémont | Major | 187 | 153 years | 770 | 616 | 80% |
| 2003 | John C. Frémont | Major | 188 | 154 years | 775 | 620 | 80% |
| 2004 | John C. Frémont | Major | 189 | 155 years | 780 | 624 | 80% |
| 2005 | John C. Frémont | Major | 190 | 156 years | 785 | 628 | 80% |
| 2006 | John C. Frémont | Major | 191 | 157 years | 790 | 632 | 80% |
| 2007 | John C. Frémont | Major | 192 | 158 years | 795 | 636 | 80% |
| 2008 | John C. Frémont | Major | 193 | 159 years | 800 | 640 | 80% |
| 2009 | John C. Frémont | Major | 194 | 160 years | 805 | 644 | 80% |
| 2010 | John C. Frémont | Major | 195 | 161 years | 810 | 648 | 80% |
| 2011 | John C. Frémont | Major | 196 | 162 years | 815 | 652 | 80% |
| 2012 | John C. Frémont | Major | 197 | 163 years | 820 | 656 | 80% |
| 2013 | John C. Frémont | Major | 198 | 164 years | 825 | 660 | 80% |
| 2014 | John C. Frémont | Major | 199 | 165 years | 830 | 664 | 80% |
| 2015 | John C. Frémont | Major | 200 | 166 years | 835 | 668 | 80% |
| 2016 | John C. Frémont | Major | 201 | 167 years | 840 | 672 | 80% |
| 2017 | John C. Frémont | Major | 202 | 168 years | 845 | 676 | 80% |
| 2018 | John C. Frémont | Major | 203 | 169 years | 850 | 680 | 80% |
| 2019 | John C. Frémont | Major | 204 | 170 years | 855 | 684 | 80% |
| 2020 | John C. Frémont | Major | 205 | 171 years | 860 | 688 | 80% |
| 2021 | John C. Frémont | Major | 206 | 172 years | 865 | 692 | 80% |
| 2022 | John C. Frémont | Major | 207 | 173 years | 870 | 696 | 80% |
| 2023 | John C. Frémont | Major | 208 | 174 years | 875 | 700 | 80% |
| 2024 | John C. Frémont | Major | 209 | 175 years | 880 | 704 | 80% |
| | | | | | | | |

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Figure 2. Mean (±SEM) TGF β Concentrations in the Controls and Patients.

The legend to Figure 2 describes the four study groups. TGF β was measured before (solid bars) and after (hatched bars) bone marrow transplantation. In Table 1, the mean of the pretransplantation TGF β values is shown. The bars are the mean, and the error bars represent the SEM. TGF β was measured in plasma by enzyme immunoassay.

After autologous bone marrow transplantation, TGF β levels fell to approximately 50 percent of their pretransplantation levels ($P<0.001$) in all three groups of patients (Table 2). To calculate the sensitivity, specificity, and positive predictive value,

After autologous bone marrow transplantation, there was a significant decrease ($P<0.001$) in the TGF β levels of patients with subsequent hepatic veno-occlusive disease or pulmonary fibrosis (Figure 2 and Figure 3). This decrease paralleled a marked decrease in the platelet count after the high-dose chemotherapy (Table 3). In contrast, the plasma TGF β levels remained unchanged ($P>0.1$) in the patients who did not have hepatic veno-occlusive disease or pulmonary fibrosis, even though their platelet counts decreased to the same extent as the counts of the patients who did have these complications. Although there was a significant difference in pretransplantation TGF β levels between the groups with hepatic veno-occlusive disease and pulmonary fibrosis and the group without these developments, as noted above, there was no significant ($P>0.1$) difference in the post-transplantation levels among these three groups.

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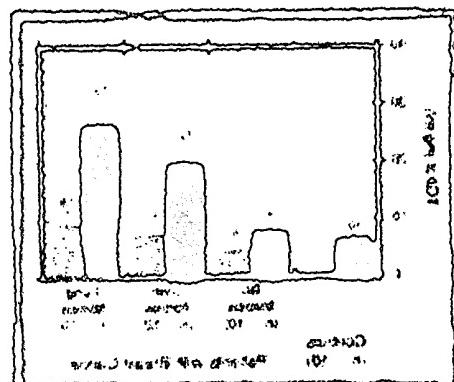
Table 2. Mean (±SEM) TGF β Levels in Plasma Before and After Autologous Bone Marrow Transplantation

[Autologous Bone Marrow Transplantation](#)

To test the usefulness of the TGF β level as an indicator of an increased risk of hepatic veno-occlusive disease or pulmonary fibrosis after high-dose chemotherapy and autologous bone marrow transplantation, the sensitivity, specificity, and the positive and negative predictive values of this marker were calculated. To make these calculations, the upper limit of normal TGF β levels in plasma was set at 10 ng per milliliter, which was 2 SD above the mean value in normal subjects (Figure 2). The resulting values (Table 4) showed that the TGF β level measured in plasma after induction chemotherapy but before high-dose chemotherapy and transplantation was a very good indicator of which patients would subsequently have pulmonary fibrosis or hepatic veno-occlusive disease (or both) after chemotherapy and transplantation. If the plasma concentration of TGF β was greater than 10 ng per milliliter, it was possible to predict with more than 90 percent accuracy that either hepatic veno-occlusive disease or pulmonary fibrosis would develop (i.e., the positive predictive value was >90 percent).

ଜୀବ ତି ଅନ୍ୟମାନଙ୍କୁ (ଏପିଟି) M12୫ ଏମ୍ ଡି ଗାନ୍ଧୀ (ଏପିଟି) M12୫ ଏମ୍ ଡି ଗାନ୍ଧୀ

ଅବ୍ୟାକ୍ତ ପରିମା ନି ପରିପୂର୍ଣ୍ଣ ହେଲା ଏବଂ ଆଶ୍ରମରେ ଯେତେବେଳେ
ଧ୍ୟାନବିନ୍ଦୁ ଦେଖିଲା ତାଙ୍କୁ ଏହା ଅମେରିକ ରୀତେ ବେଳାବେଳା
= ୩) ପରିମାର୍ଗରେ ଥିଲା ଏହା ଧ୍ୟାକ୍ତ ଏହାରେ ରେଖିନ୍ଦ୍ର
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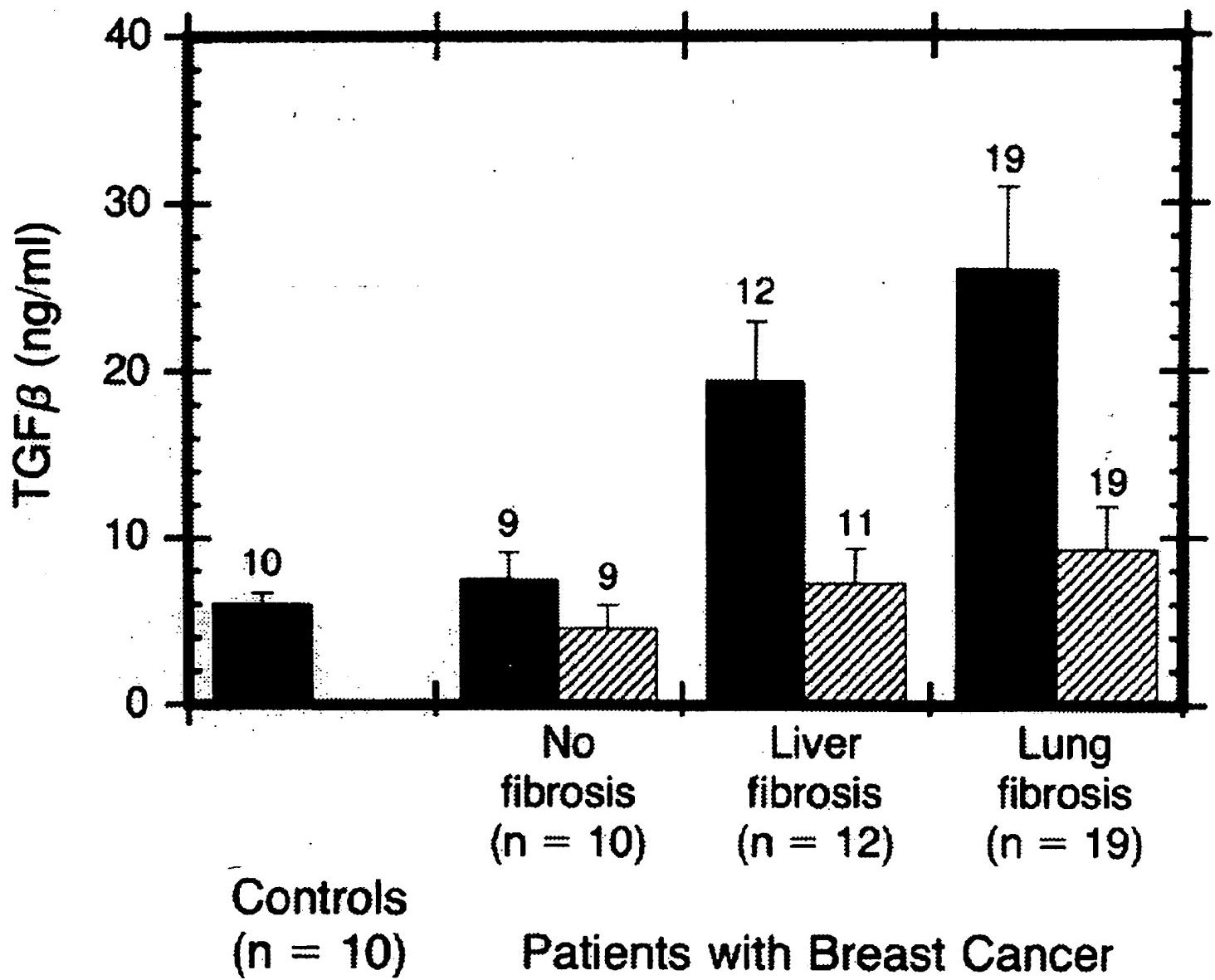


וְאֵת שָׁמֶן אֲשֶׁר־בַּיּוֹם

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To test the null hypothesis of no difference between the two groups, we can use a paired t-test. The null hypothesis is that the mean difference between the two groups is zero. The alternative hypothesis is that the mean difference is not zero. We can use a two-tailed test because we are interested in any difference, not just a specific direction. The test statistic is calculated as follows:



Ansch Fig. 3

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| VARIABLE | PATIENTS WITHOUT FIBROSIS | | PATIENTS WITH FIBROSIS | | LIVER | | LUNGS | |
|---|------------------------------|---------|------------------------|---------|----------|---------|---------|---------|
| | Before | After | Before | After | Before | After | Before | After |
| TGF β level (ng/ml)* | 7.6±1.6 | 4.6±1.4 | 19.5±3.5 | 7.3±2.1 | 26.1±4.9 | 9.3±2.6 | 6.6±1.5 | 6.6±1.5 |
| Platelet count ($\times 10^3/\text{ml}$) | 172±23 | 28±6.7 | 172±18 | 25±8.4 | 212±14 | 29±3.6 | 140±15 | 140±15 |

*To convert values to millimoles per liter; multiply by 4×10^{-8} .

Anscher Table 3

| Time | Condition | Reaction | Reaction | Reaction |
|--------|-----------|----------|----------|----------|
| 0 min | Control | None | None | None |
| 10 min | UV | None | None | None |
| 20 min | UV | None | None | None |
| 30 min | UV | None | None | None |

REFERENCES

It is also important to note that the high-level of education and income of the population is positively correlated with the level of education.

| Nombre | Apellido | Nombre | Apellido | Nombre | Apellido |
|---------|-----------|---------|-----------|---------|-----------|
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| Nombre | Apellido | Nombre | Apellido | Nombre | Apellido |
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Algunas de las piezas que se han conservado en el Museo de Arqueología de la Universidad de Costa Rica, tienen la inscripción de "Museo de Arqueología de la Universidad de Costa Rica" y "Museo de Arqueología de la UCR".

En la pieza número 002, se observa que la inscripción es "Museo de Arqueología de la Universidad de Costa Rica" y "Museo de Arqueología de la UCR".

| Nombre | Apellido | Nombre | Apellido | Nombre | Apellido |
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Table 4. Pretransplantation Concentration of Plasma TGF β as a Predictor of Liver and Lung Disease after High-Dose Chemotherapy and Autologous Bone Marrow Transplantation.

We also attempted to determine whether the development of pulmonary fibrosis or hepatic veno-occlusive disease was associated with any of the variables listed in Table 1. We could find no significant difference in the mean values for these clinical factors between the patients with these complications after transplantation and those without them ($P>0.1$ in all cases). Furthermore, there was no correlation between any of the factors and the pretransplantation TGF β levels in the three groups of patients (data not shown).

To explore the possibility that TGF β might be produced by the tumor, the relation between tumor burden, as measured by the maximal tumor dimension and the number of lymph nodes involved by cancer, and the plasma TGF β concentration before transplantation was determined (Table 5). There were no significant differences in pretransplantation TGF β levels when the patients were compared according to the number of involved lymph nodes or the greatest measurable tumor dimension (before induction chemotherapy).

[View this table:
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Table 5. TGF β Concentration at Induction Chemotherapy Before Transplantation With Liver or Lung Disease.

We also considered the possibility that patients with stage IV cancer who had previously received chemotherapy (before their enrollment in the bone marrow transplantation study) might be at increased risk for toxic complications, as compared with patients who had not previously received chemotherapy. This comparison could be made only in the group with hepatic veno-occlusive disease, since no patient in the other groups had been previously treated with chemotherapy. We found no difference ($P>0.1$) in the pretransplantation TGF β levels between the patients who had received previous chemotherapy and those who had not, which suggested that previous chemotherapy did not necessarily increase the risk of hepatic veno-occlusive disease in this group.

Discussion

Hepatic veno-occlusive disease and pulmonary fibrosis are major causes of morbidity and mortality after bone marrow transplantation for cancer. Many clinical factors define patient populations at increased risk for the development of these complications,^{12,21,22,23,24,25,26} but none of these clinical factors have been useful in assessing the risk in an individual patient. Our study indicates that the plasma TGF β concentration, if measured after induction chemotherapy, strongly correlates with the development of pulmonary fibrosis or hepatic veno-occlusive disease after high-dose chemotherapy and autologous bone marrow transplantation.

Patients most prone to pulmonary fibrosis or hepatic veno-occlusive disease after high-dose chemotherapy and autologous bone marrow transplantation have elevated TGF β levels before transplantation. A positive

10. **Digitization of the Library**: The library has started digitizing its collection. A digital catalog is available online at www.library.iitg.ac.in. The library also has a digital archive of its publications.

We also have a few more specific requirements for the new system. We would like to see the following features:

In the same way as we have seen that the clinical presentation of primary hypertension will vary according to the type of hypertension, so too will the presentation of secondary hypertension vary according to the cause.

10. Съществуващите във ФРЮИИ правни норми са създадени за да подпомагат и да улесняват правилното изпълнение на законите и правилниците във ФРЮИИ.

We also now have the ability to predict which patients will benefit from a particular treatment. This allows us to tailor treatments to individual patients, which can lead to better outcomes and reduced costs.

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In the early 1980s, the first large-scale experiments were conducted at the University of California, Berkeley, to determine the effects of different soil treatments on plant growth and yield. The results showed that the use of organic fertilizers, such as manure or compost, can significantly increase crop yields and reduce the need for chemical fertilizers.

44(1) comes in addition to the 44(1A) and 44(1B) provisions in section 44.

Io meglioio rai una diritti esistono alcuni altrimenti nulla si sarebbe mai potuto fare. Il problema è solo che ogni diritto ha un condizionante e questo è il diritto di difesa. Non c'è diritto di difesa se non c'è diritto di difesa.

equation-based models, which are often used to predict the outcome of various systems. A notable example is the model developed by the University of Cambridge, which uses a complex set of equations to predict the behavior of various systems.

| VARIABLE | LIVER FIBROSIS | LUNG FIBROSIS |
|---------------------------|-------------------|------------------|
| <i>percent</i> | | |
| Sensitivity | 75 | 74 |
| Specificity | 89 | 89 |
| Positive predictive value | 90 | 93 |
| Negative predictive value | 73 | 62 |

Anschel Table 4

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| TUMOR-BURDEN FACTOR | TGFβ (ng/ml) | P VALUE |
|----------------------------|--|----------------|
| No. of positive nodes* | | |
| ≤ 12 | 22.8 | |
| > 12 | 17.9 | >0.1 |
| Tumor size (cm)† | | |
| ≤ 3.5 | 19.4 | >0.1 |
| > 3.5 | 20.9 | |

*Mean number of positive nodes, 12.

†Mean tumor size, 3.5 cm.

Table 5. Correlation of TGF β levels with tumor burden factors. (Adapted from Anscher Table 5)

| | Abnormal | Growth |
|---------------------|-----------------|---------------|
| Normal | 22.8 | 19.4 |
| Abnormal | 17.9 | 20.9 |
| Normal vs. abnormal | 0.0001 | 0.0001 |
| Normal vs. growth | 0.0001 | 0.0001 |
| Abnormal vs. growth | 0.0001 | 0.0001 |

| 10 | 10 | 10 | 10 | 10 | 10 | 10 |
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| 99 | 99 | 99 | 99 | 99 | 99 | 99 |
| 100 | 100 | 100 | 100 | 100 | 100 | 100 |

test for TGF β has a positive predictive value of more than 90 percent for the development of either hepatic veno-occlusive disease or pulmonary fibrosis in a given patient. It may be possible to use TGF β plasma levels to individualize therapy and thus reduce the risk of both complications.

Use of TGF β in patients

We chose the assay system we used in this study because of its ability to detect very low levels of TGF β . Although enzyme-linked immunosorbent assays for the quantification of TGF β ⁴² are less sensitive than our biologic assay, our results demonstrate that enzyme-linked immunosorbent assays should have sufficient sensitivity to permit rapid screening for patients most prone to fibrotic changes (i.e., patients with plasma levels of TGF β 1 above 10 ng per milliliter [4×10^{-7} mmol per liter]).

References

The cause of elevated plasma levels of TGF β in patients who ultimately have hepatic or pulmonary fibrosis is not known. Platelets are the principal source of TGF β in humans, but an artifactual disruption of platelets seems unlikely. For TGF β levels to become falsely elevated in the patients we studied, blood samples would have had to have been obtained shortly after platelet destruction occurred, since the half-life of TGF β in the blood is only a few minutes. Also, the putative destruction of platelets by drugs or venipuncture would have had to have occurred only in the patients who ultimately had fibrosis. Finally, all patients treated with high-dose chemotherapy and autologous bone marrow transplantation had a decrease in TGF β concurrent with chemotherapy-induced thrombocytopenia.¹⁸ This finding suggests that the elevation in the plasma of the

The elevation of plasma levels of TGF β in patients with hepatic veno-occlusive disease or pulmonary fibrosis also does not appear to be related to their tumor burden. Some factor other than the tumor is apparently responsible for the elevated TGF β levels in patients with these complications.

Increased synthesis or activation of TGF β or decreased degradation of this growth factor (or some combination of these processes) is a possible response to induction chemotherapy in patients who subsequently have hepatic veno-occlusive disease or pulmonary fibrosis. Hoyt and Lazo²² have shown that strain-specific variations in TGF β messenger RNA in the lungs of mice correlate with differences in susceptibility to cyclophosphamide-induced pulmonary fibrosis. Likewise, differences may also occur in human responses to chemotherapeutic agents.

TGF β is normally secreted from cells as a glycosylated latent complex that contains phosphorylated mannose residues.⁴³ It must be dissociated from this complex to become biologically active. The latent complex of TGF β 1 binds to the receptor that accepts both glycoproteins containing mannose-6-phosphate and insulin-like growth factor II,⁴⁴ and this binding has been shown to facilitate the activation of the TGF β 1 molecule by proteolytic enzymes.⁴⁵ It is possible that this activation process is augmented in patients in whom hepatic veno-occlusive disease or pulmonary fibrosis develops, and consequently more mature TGF β would be present in the plasma. We have observed an increased concentration of TGF β in hepatocytes with increased numbers of mannose-6-phosphate-insulin-like growth factor II receptors when the liver is undergoing regeneration²² or has been exposed to the liver-tumor promoter phenobarbital.²¹ Whether a concomitant increase in the level of TGF β 1 and the number of mannose-6-phosphate-insulin-like growth factor II receptors also occurs in the liver and lungs of humans after exposure to chemotherapeutic agents, radiation, or other insults resulting in fibrosis is unknown.

Supported by grants (CA460172 and CA-25957) from the National Cancer Institute (Bethesda).

Received June 1, 1993; accepted July 20, 1993; revised August 24, 1993; and accepted September 1, 1993.

வாய்மையினால் முன் கொண்டு வரும் நிலைத்திறன் என்பதை அறிய வேண்டும்.

ବ୍ୟାକିଲ୍ଲ ପାଇଁ ଏଣ୍

W e can see that the Fe^{2+} concentration in the solution increases as time goes by. This is because the iron ions are being reduced from Fe^{3+} to Fe^{2+} . The concentration of Fe^{3+} decreases over time, which means that the reaction is proceeding in the forward direction.

After being exposed to the *Plague*, *Spurred by a desire to help others*, *he turned out as best he could* (Fig.). The debris left over from his work was collected and used to fill the gap with a mixture. In group 24.1 (ab. 211, 2 weeks) the *Spurred by a desire to help others* mixture, etc., was used to fill both other rooms, leaving no

Constitutes to generate a simulation system which is able to generate the simulation data to measure the effect of the different test methods.

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222 Since top surface (G) has to make it to work, it has to move up to meet the top. Therefore
the first thing we have to do is to move the top surface (G) up to the top. This is done by
the first two moves of the algorithm.

iii. *Paracoccidioides brasiliensis* (A. da Motta et al.)

11. **W**hile the **U**nited **S**tates **W**ay **s**aid **o**ut **in** **R**ussia, **W**hich **U**nited **S**tates **W**ay **s**aid **o**ut **in** **R**ussia.

Fig. 1. Afferent villus-globoid groups of adrenocortical cortex (from a 10-year-old boy).

1. *Constitutive equations for the shear modulus and wave velocity of a two-phase medium*, by G. C. Sih and R. D. Cook.

in December 2018, the first 1000 units were delivered to the market.

in unexpended amounts remaining to be expended in the fiscal year in which they were incurred.

in 1910 to all his friends he wrote: "I am now in Mexico at Guanajuato where I have been working on my book on the Mexican Revolution."

३८५ अनुवाद विजय कुमार शर्मा

and the members of the executive committee to reduce all fees by 10% to level with the rest of the industry.

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Consequently, the author's claim that the study is "not applicable" to the present situation is misleading.

We are grateful to the following for technical assistance, to Denise Crawford for assistance in data acquisition, to Richard Dodge for statistical advice, and to Roxanne Scroggs for assistance in the preparation of the manuscript.

Michael N. Anacker, M.D.
John D. Muller, M.D.
Jeffrey S. Jacobs, M.D.
David J. Johnson, M.D.
John C. Hwang, M.D.
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It was the intention of the author to include a detailed description of the methods used in this study, but this would have greatly increased the size of the paper.

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the following recommendations are made:

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5. *Chloromyces* M. H. Nees var. *Spumifer* (C. M. Smith) Sacc.

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clipper sailing ship built by Captain John

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To extend temporary protection to foreign firms now doing business in the U.S.

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gratia et amicorum et voluntate diversorum patrum et consiliorum. Et quod
dicitur de laudibus omniisque virtute.

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